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Clarence Lee, *Howard University*
Yvonne Hogan
Georgiana Aboko-Cole

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Clarence M. Lee, PhD, Yvonne Hogan, MS, and Georgiana F. Aboko-Cole, PhD
Washington, DC

Malaria, the number one disease in the world, is caused by intracellular protozoans belonging to the Subphylum, Sporozoa; Suborder, Haemosporidia; and Family, Plasmodiidae. The four classical organisms producing disease in man are Plasmodium vivax, P. falciparum, P. malariae, and P. ovale. Although malaria has been known to man for centuries, attempts are still being made to control and eliminate its devastating effects in tropical and subtropical areas of the world. Current active interest in malarial immunology and immunopathology derives from two main facts: (1) that human malaria is still one of the chief health problems in a broad tropical and subtropical zone in which lie most of the developing countries; and (2) most of the seminal leads in basic immunology are being applied to malarial immunology, either directly in human patients, or using laboratory animals as test objects.

This paper addresses the nature of malarial immunity and target organs in malarial pathology.

Plasmodia consists of an array of heterogeneous antigenic components whose molecular weights range between 60,000 and 90,000 for human plasmodia, from 8,000 to 130,000 for rodent plasmodia, and may reach 700,000 for avian plasmodia. Some of the antigens are proteins, glycoproteins, or membrane-associated phospholipids.

More than 30 distinct antigens have been identified in association with the blood forms of P. falciparum and antibodies of corresponding specificity have been detected in sera obtained from Gambian residents in hyperendemic areas. Wilson et al. have classified these antigens into three main groups: L (labile), R (resistant), and S (stable) on the basis of their ability to withstand heating, and have further divided these classes into subgroups on the basis of other factors (La1 and La2, Lb, R1, and R2, S1 and S2). Not all antigens of P. falciparum are equally immunogenic. La antigens appear to be good immunogens since antibodies to them can be demonstrated, in high titre, in sera taken from all age groups in hyperendemic areas. On the other hand, S antigens often failed to induce a detectable antibody response in heavily parasitized children, and when responses did occur they were weak and transient. In more recent studies, the gel diffusion test was used to detect antibodies to malarial S antigens in sera of young Gambian children. Antibodies tended to appear more swiftly when antigen was lost rapidly from the circulation. Observations made on individual responses indicated antibody production was influenced by factors other than the intrinsic properties of antigens, such as genetic ability to respond, immunological competence, and malarial experience. R1 antigen has been identified in all extracts of P. falciparum parasites examined by Wilson and his colleagues, yet antibodies to them have been found in only one of thousands of immune sera studied.

Plasmodial antigens at the surface of the infected erythrocyte or of the parasite are suspected of being strain specific, and therefore possibly of being associated with strain specific protection. In addition to blood stage antigens, stage-specific sporozoite antigens exist and have been investigated. The fact that only mature sporozoites are highly infective suggests a possible relationship between antigen and infectivity. Stage of maturation and antigenic modulation in response to antibody may contribute to the antigenic variability of Plasmodium.

According to the studies of Mitchell et al., stage specific antigens associated with merozoites are vulnerable to neutralizing antibody, which is thought to interfere with the attachment of merozoites to specific receptor sites on susceptible erythrocytes. Since plasmodia consist of numerous antigens, it is to be expected they would induce multiple antibody reactions. With the aid of radial immunodiffusion in agar and comparative immunoelectrophoresis, both employing antibody raised against specific immunoglobulin (Ig) categories, the dynamic changes in serum Ig levels can be followed. In the sera studied, protective antibody was associated with both IgG and IgM, but not with IgA or IgE.

Ig production increase is manifold during malarial infection, but much of the Ig produced is not antiplasmodial antibody, and little of the specific antibody protective. In the sera studied, protective antibody was associated with both IgG and IgM, but not with IgA or IgE. Antiplasmodial protection in human malaria is generally associated with raised levels of IgG. Population studies in Gambia have shown
malarial parasitemia to be associated with elevated levels of IgG over the first 20 years of life, but with elevated IgM levels over only the first two years.6

The factors that determine the Ig class of antibodies synthesized are not known, but age, immunocompetence, and previous exposure are probably important.2,3

Course of Infection

According to Voller,18 under natural conditions malaria infections are initiated when an infected mosquito injects sporozoites as it feeds. The sporozoites circulate for only a few minutes before becoming localized in the liver, where development of pre- and exoerythrocytic forms take place. There seems to be no immunological response to the injected viable sporozoites under natural conditions. This is rather surprising as it has been shown that injected sporozoites, modified by radiation or chemical treatment, can lead to serological response and to the development of immunity to subsequent challenge by viable sporozoites.11,19

Pre- and exoerythrocytic forms developing in the liver seem to evoke no immunological response until they reach maturity. Voller18 reported that at the time of rupture of the tissue schizont, polymorphonuclear leukocytes invade the site, followed by other cellular infiltrates, which decline in a short time. No serum antibodies are detectable at the time. It is only when invasion of the blood occurs that the full immunopathological response is initiated. Each asexual cycle of parasitemia consists of trophozoites forming schizonts, each containing merozoites which are released on rupture of the host cell to infect more red cells.20

In most malaria infections, the theoretical rate of multiplication is rarely reached due to removal of the parasites and infected cells by phagocytic activities in the spleen. The parasitemia increases up to a certain point then decreases abruptly. The point where the host’s defenses gain control is known as the crisis and leads to the drop in parasitemia. Crisis is characterized by intense reticuloendothelial hyperplasia and reactivity, with many of the macrophages being loaded with malarial pigment and other products resulting from phagocytic activity.21 The phagocytosis is not just an increase in the nonspecific activity of macrophages, but a specific immunological process. The immunological processes involved opsonization, agglutination, and precipitation reactions.5,22,23

Synergism between cells and antibody is suggested in immune mechanisms against malarial asexual cycles (merozoites) in the blood,12 with primary mediation by specific IgG antibodies.6 Complement is frequently involved in the process.24 According to Cohen et al,16 cell-mediated immunity has no defined role in specific malarial immunity. Under natural conditions survival of parasites in the immunized host (acquired immunity) is related to reinfection with distinct strains of the species or represents a relapse derived from persistent pre-erythrocytic stages of the Plasmodium. It may also be related to soluble immune complexes or free antigens blocking the action of the antibody, or be connected with the organism’s ability to undergo antigenic variation.24

Immunopathology

McGregor2 finds that malaria often elicits serological responses which, in temperate zones, are usually associated with connective-tissue disease. This may be due to (a) release of cross-reacting antigen or (b) alteration of host tissue, thus rendering it antigenic. In either case, Mathews et al25 postulate that this leads to production of antibodies which react with their substrates.

The majority of all sera of adults in malarious areas contain heterophile agglutinins of IgM class that react with foreign erythrocytes in vitro, or even with trypsinized human erythrocytes. Rheumatoid factor, an antiglobulin, usually to IgG, is also common in malarious areas and the titres in adults often correlate with their malarial antibody levels.26,27

The first hint that malaria might affect the immune response to unrelated antigens was provided by McGregor,6 who showed that malaria-infected persons responded less well to tetanus toxoid injections. Greenwood et al27 pursued this and found that some humoral but not cell-mediated responses were depressed and that the depression was greatest in those individuals with high parasitemia. Targett28 has put forward a theory that trypanosome infections may interfere with the cooperation of T- and B-lymphocytes and also lead to excessive production of partially nonspecific IgM and to immunodepression of other immune responses that require T- and B-cell cooperation. Topley et al29 believe that malarial immunosuppression is basically due to the same mechanism as postulated for trypanosomiasis.

Malarial immunodepression has received much attention recently in the context of what it might mean in terms of other diseases. Greenwood et al30 speculated that the apparent rarity of some autoimmune diseases in the tropics might be related to immunological disturbances produced by malaria. Support for this point of view has come from experimental work in which it was shown that some diseases, thought to be of autoimmune origin, which occur spontaneously in some strains of mice, could be delayed by infecting the animals with malarial organisms.

Of particular interest in the immunopathological sense is what a variety of authors have considered to be an identifiable entity and have termed the "tropical splenomegaly syndrome" or "big spleen disease," and which they consider to be associated with malaria.27,30

An apparently identical disease has been reported from areas of East and West Africa, India, and New Guinea where malaria is endemic.27 It is claimed that this is a discrete syndrome, the characteristics of which include massive chronic splenomegaly associated with lymphocytic infiltration of hepatic sinusoids and high serum levels of IgM and malarial antibodies. Affected individuals, although often living in areas of highly edematous malaria, do not have higher than usual parasite rates or densities, but long-term antimalarial therapy does lead to a reduction in their spleen size.31 It has been suggested that patients with tropical splenomegaly syndrome have an aberrant, although effective, immune response to malaria. The sera of these patients contain large amounts of IgM in addition to high levels of antiglobulins and hemagglutinins.27,30

It is probable that more immunopathological sequels to malaria, combined with other agents, will be identified in the future. It is well known, too, that accidental contamination of animal malaria parasite
strains with viruses eperythrozoon, Haemobartonella, or Mycoplasma can easily occur and the course of a malaria infection and its pathology can then be altered.\textsuperscript{32}

Literature Cited


1979 NMA Convention

The 84th annual convention and scientific assembly of the National Medical Association will be held in Detroit, Michigan from July 29—August 2, 1979.

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